Claims

1. (currently amended) A heterologous fusion protein comprising a GLP-1 analog ~~comprising a sequence selected from the group consisting~~ of:

~~a)~~ (SEQ ID NO:1)

His-Xaa$_8$-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Gly

wherein Xaa$_8$ is ~~selected from~~ Gly ~~and Val~~;

~~b) (SEQ ID NO:2)~~

~~His-Xaa$_8$-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly-Gly~~

~~wherein Xaa$_8$ is selected from Gly and Val;~~

~~c) (SEQ ID NO:3)~~

~~His-Xaa$_8$-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Pro~~

~~wherein Xaa$_8$ is selected from Gly and Val;~~

~~d) (SEQ ID NO:4)~~

~~His-Xaa$_8$-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly-Pro~~

~~wherein Xaa$_8$ is selected from Gly and Val;~~

~~e) (SEQ ID NO:5)~~

~~His-Xaa$_8$-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly~~

~~wherein Xaa$_8$ is selected from Gly and Val;~~

~~f) (SEQ ID NO:6)~~

~~His-Xaa$_8$-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly~~

~~wherein Xaa$_8$ is selected from Gly and Val;~~

fused to the Fc portion of an immunoglobulin ~~comprising the sequence~~ of SEQ ID NO:7

Ala-Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Cys-Pro-Pro-Cys-Pro-Ala-Pro-Xaa$_{16}$-Xaa$_{17}$-Xaa$_{18}$-Gly-Gly-Pro-Ser-Val-Phe-Leu-Phe-Pro-Pro-Lys-Pro-Lys-Asp-Thr-Leu-Met-Ile-Ser-Arg-Thr-Pro-Glu-Val-Thr-Cys-Val-

Val-Val-Asp-Val-Ser-Gln-Glu-Asp-Pro-Glu-Val-Gln-Phe-Asn-Trp-Tyr-Val-Asp-Gly-Val-Glu-Val-His-Asn-Ala-Lys-Thr-Lys-Pro-Arg-Glu-Glu-Gln-Phe-Xaa_{80}-Ser-Thr-Tyr-Arg-Val-Val-Ser-Val-Leu-Thr-Val-Leu-His-Gln-Asp-Trp-Leu-Asn-Gly-Lys-Glu-Tyr-Lys-Cys-Lys-Val-Ser-Asn-Lys-Gly-Leu-Pro-Ser-Ser-Ile-Glu-Lys-Thr-Ile-Ser-Lys-Ala-Lys-Gly-Gln-Pro-Arg-Glu-Pro-Gln-Val-Tyr-Thr-Leu-Pro-Pro-Ser-Gln-Glu-Glu-Met-Thr-Lys-Asn-Gln-Val-Ser-Leu-Thr-Cys-Leu-Val-Lys-Gly-Phe-Tyr-Pro-Ser-Asp-Ile-Ala-Val-Glu-Trp-Glu-Ser-Asn-Gly-Gln-Pro-Glu-Asn-Asn-Tyr-Lys-Thr-Thr-Pro-Pro-Val-Leu-Asp-Ser-Asp-Gly-Ser-Phe-Phe-Leu-Tyr-Ser-Arg-Leu-Thr-Val-Asp-Lys-Ser-Arg-Trp-Gln-Glu-Gly-Asn-Val-Phe-Ser-Cys-Ser-Val-Met-His-Glu-Ala-Leu-His-Asn-His-Tyr-Thr-Gln-Lys-Ser-Leu-Ser-Leu-Ser-Leu-Gly-Xaa_{230} ~~(SEQ ID NO:7)~~

wherein:

Xaa at position 16 is ~~Pro or~~ Glu;

Xaa at position 17 is ~~Phe, Val, or~~ Ala;

Xaa at position 18 is ~~Leu, Glu, or~~ Ala;

Xaa at position 80 is Asn~~ or Ala~~; and

Xaa at position 230 is Lys or is absent;

and further comprising a peptide linker of SEQ ID NO:8
Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser
wherein the peptide linker is between the C-terminal glycine residue of the GLP-1 analog and the N-terminal alanine of the Fc portion.

2. (withdrawn) The heterologous fusion protein of Claim 1 wherein the C-terminal glycine residue of the GLP-1 analog is fused to the N-terminal alanine residue of the Fc portion via a peptide linker comprising a sequence selected from the group consisting of:

a) Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO:8);

b) Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO:19); and

c) Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO:21).

3. (withdrawn) The heterologous fusion protein of Claim 2 wherein the linker comprises the sequence of SEQ ID NO:8.

4. (withdrawn) The heterologous fusion protein of any one of Claims 1 to 3 wherein Xaa at position 8 of the GLP-1 analog is Gly.

5. (withdrawn) The heterologous fusion protein of any one of Claims 1 to 3 wherein Xaa at position 8 of the GLP-1 analog is Val.

6. (withdrawn) The heterologous fusion protein of any one of Claims 1 to 3 wherein the GLP-1 analog comprises the sequence of SEQ ID NO:1.

7. (withdrawn) A heterologous fusion protein selected from the group consisting of: a) Gly^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-1L-IgG4 (S228P); b) Gly^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-1L-IgG4 (S228P, F234A, L235A); c) Gly^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-1L-IgG4 (S228P, N297A); d) Gly^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-1L-IgG4 (S228P, F234A, L235A, N297A); e) Gly^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-1.5L-IgG4 (S228P); f) Gly^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-1.5L-IgG4 (S228P, F234A, L235A); g) Gly^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-1.5L-IgG4 (S228P, N297A); h) Gly^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-1.5L-IgG4 (S228P, F234A, L235A, N297A); i) Gly^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-2L-IgG4 (S228P); j) Gly^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-2L-IgG4 (S228P, F234A, L235A); k) Gly^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-2L-IgG4 (S228P, N297A); l) Gly^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-2L-IgG4 (S228P, F234A, L235A, N297A); and the des-K forms thereof.

8. (withdrawn) A heterologous fusion protein selected from the group consisting of: a) Val^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-1L-IgG4 (S228P); b) Val^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-1L-IgG4 (S228P, F234A, L235A); c) Val^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-1L-IgG4 (S228P, N297A); d) Val^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-1L-IgG4 (S228P, F234A, L235A, N297A); e) Val^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-1.5L-IgG4 (S228P); f) Val^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-1.5L-IgG4 (S228P, F234A, L235A); g) Val^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-1.5L-IgG4 (S228P, N297A); h) Val^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-1.5L-IgG4 (S228P, F234A, L235A, N297A); i) Val^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-2L-IgG4 (S228P); j) Val^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-2L-IgG4 (S228P, F234A, L235A); k) Val^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-2L-IgG4 (S228P, N297A); l) Val^{8}-Glu^{22}-Gly^{36}-GLP-1(7-37)-2L-IgG4 (S228P, F234A, L235A, N297A); and the des-K forms thereof.

9.-15. (cancelled)

16. (withdrawn) A method of treating a patient with non-insulin dependent diabetes mellitus comprising the administration of a therapeutically effective amount of the heterologous fusion protein of any one of Claims 1 to 8.

17. (withdrawn) A method of inducing weight loss in an overweight patient comprising the administrations of a therapeutically effective amount of the heterologous fusion protein of any one of Claims 1 to 8.

18. (withdrawn) The method of Claim 16 or 17 wherein the heterologous fusion protein is administered at a dose between about 0.05 mg/kg to 0.5 mg/kg body weight.

19. (withdrawn) The method of Claim 16 or 17 wherein the heterologous fusion protein is administered once a week.

20.-24. (cancelled)

25. (withdrawn) A method of treating a patient with non-insulin dependent diabetes mellitus comprising the administration of a therapeutically effective amount of the heterologous fusion protein of any one of Claims 1 to 8, wherein the fusion protein stimulates insulin secretion, inhibits glucagon secretion, inhibits gastric emptying, inhibits gastric or intestinal motility, or induces weight loss.

26. (new) A heterologous fusion protein comprising a GLP-1 analog of (SEQ ID NO:1)

His-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Gly

wherein Xaa_8 is Gly;

fused to the Fc portion of an immunoglobulin of SEQ ID NO:7

Ala-Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Cys-Pro-Pro-Cys-Pro-Ala-Pro-Xaa_{16}-Xaa_{17}-Xaa_{18}-Gly-Gly-Pro-Ser-Val-Phe-Leu-Phe-Pro-Pro-Lys-Pro-Lys-Asp-Thr-Leu-Met-Ile-Ser-Arg-Thr-Pro-Glu-Val-Thr-Cys-Val-Val-Val-Asp-Val-Ser-Gln-Glu-Asp-Pro-Glu-Val-Gln-Phe-Asn-Trp-Tyr-Val-Asp-Gly-Val-Glu-Val-His-Asn-Ala-Lys-Thr-Lys-Pro-Arg-Glu-Glu-Gln-Phe-Xaa_{80}-Ser-Thr-Tyr-Arg-Val-Val-Ser-Val-Leu-Thr-Val-Leu-His-Gln-Asp-Trp-Leu-Asn-Gly-Lys-Glu-Tyr-Lys-Cys-Lys-Val-Ser-Asn-Lys-Gly-Leu-Pro-Ser-Ser-Ile-Glu-Lys-Thr-Ile-Ser-Lys-Ala-Lys-Gly-Gln-Pro-Arg-Glu-Pro-Gln-Val-Tyr-Thr-Leu-Pro-Pro-Ser-Gln-Glu-Glu-Met-Thr-Lys-Asn-Gln-Val-Ser-Leu-Thr-Cys-Leu-Val-Lys-Gly-Phe-Tyr-Pro-Ser-Asp-Ile-Ala-Val-Glu-Trp-Glu-

Ser-Asn-Gly-Gln-Pro-Glu-Asn-Asn-Tyr-Lys-Thr-Thr-Pro-Pro-Val-Leu-Asp-Ser-Asp-Gly-Ser-Phe-Phe-Leu-Tyr-Ser-Arg-Leu-Thr-Val-Asp-Lys-Ser-Arg-Trp-Gln-Glu-Gly-Asn-Val-Phe-Ser-Cys-Ser-Val-Met-His-Glu-Ala-Leu-His-Asn-His-Tyr-Thr-Gln-Lys-Ser-Leu-Ser-Leu-Ser-Leu-Gly-Xaa_{230}

wherein:

Xaa at position 16 is Glu;

Xaa at position 17 is Ala;

Xaa at position 18 is Ala;

Xaa at position 80 is Asn; and

Xaa at position 230 is absent;

and further comprising a peptide linker of SEQ ID NO:8

Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser

wherein the peptide linker is between the C-terminal glycine residue of the GLP-1 analog and the N-terminal alanine of the Fc portion.